REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

Claims 1-12 are currently pending. Claims 1-12 are amended herein. Claims 2-12 are amended to place the claims in better American format and to remove alternative language from claims 8-10. The optional subject matter of claims 8-10 has been made the subject of new claims 29-31. New dependent claims 16-28 are added herein to further claim specific embodiments of the invention as recited in the specification. Basis for the amendments and new claims may be found throughout the specification and claims as-filed, especially at page 5, line 17, page 8, lines 9-38, page 10, lines 20-34, page 11, lines 2-13, page 12, line 37 to page 13, line 6 and claims 8-10.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-12 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite. The Examiner argues that the claims remain vague and indefinite for reciting claim limitations for the recitation of employing the term "about".

In the interest of expediting the prosecution and without acquiesing with the rejection, independent claim 1 is amended herein to remove the recitation of "about". Thus, this rejection is obviated.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-12 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Kameyama *et al.* in view of Gao and Wilson. The Office Action states that Kameyama *et al.* disclose methods for the inactivation of enveloped viruses that are contaminating a protein-containing composition by treating said compositions with 0.3% (w/v) TNBP and 1% (w/v) Tween 80. Gao and Wilson purportedly disclose the medical importance of adenoviral vectors and their use in therapeutic compositions. The Office Action states that it would have been obvious to the skilled artisan to subject viral preparations comprising both enveloped viruses and non-enveloped adenoviruses to the aforementioned treatments, since this would provide a means of ensuring the safety of non-enveloped adenoviral vector preparations for any one of a number of purposes such as gene therapy or diagnostic applications. Applicants traverse, with regard to the rejected claims and the new claims.

In order to establish a case of *prima facie* obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See* M.P.E.P. §2142. Applicants respectfully submit that these criteria have not been met in the present Office Action.

The Office Action states that it would have been obvious to the skilled artisan to subject adenoviral preparations contaminated with enveloped viruses to the TNBP-Tween

80 treatment disclosed by Kameyama *et al.* in connection with protein-containing preparations, because this would provide a means of ensuring the safety of the adenoviral preparations for any one of a number of purposes, such as gene therapy or diagnostic applications.

However, Applicants note that Kameyama *et al.*, the primary reference, provide a process for producing a virus-inactivated protein composition using a mixture of TNBP and Tween 80. The process was experimented on blood-derived protein preparations contaminated with both enveloped (VSV and Sindbis) and non enveloped (Echo) viruses. Enveloped VSV and Sindbis viruses were inactivated after 1 hour period of time whereas the Echo viruses remain infective. Gao and Wilson describe in very general terms the potential use of adenoviral vectors as gene therapy vectors.

Thus Applicants submit that there is no motivation in the prior art that would lead the skilled artisan to combine the cited references in such a way to produce the process as claimed, especially a process which preserves at least 80% of the adenovirus activity. To this end, independent claim 1 is amended herein to recite that the process of claim 1 preserves at least 80% of the adenovirus activity.

None of the references, alone or in combination, disclose or even suggest the problem of contamination of adenoviral preparations by enveloped viruses. Kameyama *et al.* discuss the resistance of non enveloped Echo viruses to TNBP/Tween treatment in protein-containing preparations. Gao and Wilson, the secondary references, neither teach nor even address the problem of the contamination of the adenoviral stocks by enveloped

viruses. In fact, in contrast, these references refer to routine procedures to produce the viral stocks, *i.e.,* after assembly and construction, the adenovirus vectors are packaged in the E1/E4-expressing cell line, the virion particles are harvested from the cell extract and purified by buoyant density ultracentrifugation in a CsCl gradient (as disclosed on column 9, lines 37-51).

Further, Kameyama *et al.* fail to provide any suggestion that the TNBP/Tween treatment could be successfully carried out to purify adenovirus preparations. The reference certainly fail to disclose, suggest or provide motivation for the enveloped contaminants be inactivated, whereas the recovered adenovirus remain sufficiently infective to achieve its therapeutic effect.

Thus, there is no motivation or expectation of success for the skilled artisan, who would have no reason to believe that the TNBP and Tween treatment will function equally well in connection with adenoviral preparations as it does when used with Echo virus-containing protein preparations. Applicants note that this is particularly true in view of the differences of structure and stability that exist between these two non-enveloped viruses. The Office Action does not provide an explanation as to why the skilled artisan would consider these two different types of viruses to have identical properties, whereas Applicants have shown that they are have differencies in structure and stability that would lead the skilled artisan to believe the two viruses are identical.

To provide further evidence in this regard, Applicants note that a stable virus such as Echo virus might be expected to be particularly resistant to the TNBP/Tween treatment

whereas a "somewhat fragile" virus such as adenovirus (as mentioned in Huygues *et al.*, *Human Gene Ther.*, 6: 1403-1416 (1995), as submitted by Applicant on April 28, 2003) is more likely to be altered by such a treatment. To this end, Applicants provide a showing that inactivation of Echo viruses can be reversed by the presence of some organic compounds (*see* page 550 of *Virology 2nd Ed.*, Fields *et al.*, Raven Press, as submitted by Applicant on April 28, 2003). Applicants emphasize that blood-derived products are complex protein preparations that are susceptible to contain such "stabilizing" extraneous organic compounds (*e.g.*, serum albumin) that may protect Echo viruses from inactivation by TNBP-Tween treatment.

Applicants further draw the Examiner's attention to the experimental data provided on page 8 of Kameyama *et al.* and in particular to Tables 2 to 4. Here, Kameyama et al. illustrate the differences in Echo virus stability according to the original protein preparation. As shown in Table 3, TNBP/Tween 80 treatment does not adversely affect the viral activity of Echo viruses present in Factor IX-containing DEAE eluate since the viral titer remain stable for at least 30 min of incubation. However, as illustrated in Tables 2 and 4, a weak but significant inactivating effect is observed following TNBP/Tween 80 treatment of FVIII cryoprecipitate and fibrinogen preparation. Applicants note that a one log decrease of Echo virus titer present in FVIII preparation was observed as soon as after 30 min of incubation and more than a 2 log reduction after 240 min (*see* Table 2).

Similarly, a gradual reduction of Echo virus activity over time was detected following TNBP/Tween treatment of fibrinogen preparation (*see* Table 4). Applicants note

that a 2 log reduction of a viral titer during one step of a purification procedure would be incompatible with an industrial process.

In marked contrast to what is disclosed in the cited references, the presently claimed process permits inactivation of enveloped virus contaminants while preserving the infectivity of the adenovirus of therapeutic interest. As demonstrated in the Examples of the present application, the adenovirus titer is not adversely affected - and even improved - after the TNBP/Tween treatment. The improvement of adenovirus infectivity is due to the action of the solvent on virus aggregates. Therefore, the method claimed by the present invention is of great importance in the field of adenovirus-mediated gene therapy, as it is the first method to provide safer adenoviral preparations that are free of potentially harmful enveloped viruses and that can be used routinely in clinical settings.

In light of the amendments to the claims and in light of the above remarks, Applicants submit that the claims (the pending claims and new dependent claims 16-31) are patentable over the cited references. Applicants request that the rejections under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

In the event any further fees are due to maintain pendency of this application, the Examiner is authorized to charge such fees to Deposit Account No. 02-4800.

Respectfully submitted,

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